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SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/851,965	05/06/97	YOUNG	224/142

HM11/0609

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EXAMINER	
CELSA, B	
ART UNIT	PAPER NUMBER
1654	4

DATE MAILED: 06/09/98

Please find ~~below a~~ attached communication from the EXAMINER in charge of this application.

Commissioner of Patents

file copy

Office Action Summary

Application No.	Applicant(s)
08/851,965	Young et al.
Examiner	**Group Art Unit**
Bennett Celsa	1654

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-12* _____ is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-12* _____ is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☒ NOTICE TO COMPLY WITH SEQUENCE DISCLOSURES

--- *SEE OFFICE ACTION ON THE FOLLOWING PAGES* ---

DETAILED ACTION

Claims 1-12 are currently pending.

Drawings

1. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

Specification

2. The disclosure is objected to:

a. Due to an incomplete reference to a provisional application (e.g. see page 25, lines 17-20) which lacks the application number. AND

b. Because of improper incorporation by reference. The attempt on page 11 (lines 1-16); page 19 (lines 19-27); page 20 (line 27) to page 21 (line 4) to incorporate "essential" (e.g. to description and/or enablement under 35 USC 112, first paragraph) subject matter into this application to prior U.S. application(s) [especially those which incorporated by reference to another application] or PCT application(s) by reference is improper because an application as filed must be complete in it self in order to comply with 35 U.S.C. 112. Additionally, the citation of peptides by name or designation *other than by primary peptide sequence* (See e.g. 25,28,29 Pro h-amylin or 18 Arg25,28Pro-h-amylin: specification at pages 13 and 14 AND peptides of claim 7) which are within the scope of the sequence rules, REQUIRES compliance with the sequence rules, failure of which, would constitute an improper incorporation by reference of essential subject matter. Recall that "Essential material" is defined as that which is necessary to (1)

describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe the best mode (35 U.S.C. 112). In any application which is to issue as a U.S. patent, essential material may not be incorporated by reference to (1) patents or applications published by foreign countries or a regional patent office, (2) non - patent publications, (3) a U.S. patent or application which itself incorporates "essential material" by reference, or (4) a foreign application. See In re Fouche , 439 F.2d 1237, 169 USPQ 429 (CCPA 1971). See MPEP 608.01P. Applicant is required to amend the disclosure to include the material incorporated by reference and comply with the Sequence Rules regarding applicable peptide sequences. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. E.g. See In re Hawkins , 486 F. 2d 577, 179 USPQ 167 (CCPA 1973).

Noncompliance With Sequence Rules

It is noted that the present application contains peptide sequences (e.g. tetrapeptides or greater) which fail (e.g.see pages 15-20) to conform to the Sequence Disclosure Rules found in 37 CFR 1.821-1.825. See the Attached Notice To Comply.

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1, 2 and 5 are rejected under 35 U.S.C. 102(a) as being anticipated by WPIDS Abstract No. 98-019088 to Liu et al. CN 1133718 (10/96). The Abstract discloses a pharmaceutical composition comprising amylin which when administered to a human cures gastrosis (e.g. gastritis and gastric ulcer) with a 90% total effective rate and a 50% cure rate without toxic side effects.

5. Claims 1, 2, 5 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over WPIDS Abstract No. 98-019088 to Liu et al. CN 1133718 (10/96).The Abstract discloses a pharmaceutical composition comprising amylin which when administered to a human cures gastrosis (e.g. gastritis and gastric ulcer) with a 90% total effective rate and a 50% cure rate without toxic side effects. Although, the Abstract discloses the administration, in general, of an amylin composition to cure gastrosis (e.g. prevent and/or treat) the abstract is silent as to a specific mode of administration (e.g. buccal, oral etc.). The WPIDS Abstract provides clear motivation for the skilled artisan to prepare pharmaceutical dosage formulations for administration to prevent/treat gastrosis. The making of pharmaceuticals and the determination of optimum delivery dosages and means of administration is within the skill of the art. Accordingly, the making and use of pharmaceutical dosage formulations for various modes of administration of pharmaceuticals containing amylin for treating/prevention gastrosis would have been prima facie obvious to the skilled artisan at the time of applicant's invention in view of the WPIDS Abstract teaching..

6. Claims 1-2 and 5-8 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Kolterman et al., WO 95/07098 (3/95)..

Kolterman et al. disclose the administration of "amylin" or "amylin agonists", especially "amylin agonist analogues" which are preferred (e.g. see pages 29-30) and tri-pro h-amylin which is most preferred (see tripro 25,28,29 human amylin, AKA AC-0137: See e.g. page 21 under

"Summary of the Invention") for reducing gastric motility and slowing gastric emptying (e.g. See Abstract and PCT claims). In a preferred embodiment, AC-O137 is administered to humans (e.g. by placebo, infusion or by an IV bolus) over a wide range of dosages that are within the scope of the presently claimed invention. (E.g. see pages 24-25 and disclosed figures). The mode of administration (e.g. parenteral, nasal and oral: see page 42); the amounts administered (e.g. see pages 44-45) and the preferred (e.g. amylin analogues) and most preferred compounds (e.g. tri pro amylin analogues) are within the scope of the presently claimed invention. The actual administration to humans of compounds (e,g, AC-O137) in dosages within the scope of the presently claimed invention would necessarily anticipate the presently claimed invention drawn to the prevention of gastritis/ulcers. Additionally, the reference teaching of the administration of tri pro h-amylin to humans in amounts within the scope of the presently claimed invention directly anticipates and further anticipates (e.g.by immediately envisaging) the selection of the selection of the preferred h-amylin analogues disclosed in the reference due to the small list e.g. 20 or less (e.g.see page 29-30) and page 45 listing the top 7 amylin analogues or alternatively renders obvious the selection of the preferred amylin analogues for use in the disclosed method. Accordingly, the reference method of reducing gastric motility and slowing gastric emptying (or any of the other reference methods) serves to inherently "prevent" or alternatively would be expected to prevent gastritis (or ulceration) because the *same peptide(s)* is applied in the *same way (e.g. administered in the same way to the same host)* in the *same amount*. *In re Best*, 195 USPQ 430,433 (CCPA 1977); *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993).

7. Claims 1-3, 5-6, 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evans et al., U.S. Pat. No. 4,530,838 (7/85), Gray et al, Annals of Surgery, Vol. 219 No. 1 pages 58-64, CAPLUS AN 1987:79162 to Maggi et al., Gen. Pharm. (1987) Vol. 18(1) pages 33-4 and Gheczy et al, U.S. Pat. No. 4,528,193 (7/85).

The presently claimed invention encompasses the use of "amylin agonists" which include Calcitonin Gene Related peptide (CGRP) for its gastric protective effect (e.g. treat gastritis or gastric ulceration). The presently claimed invention includes the concomitant administration of an amylin agonist with a nonsteroidal antiinflammatory agent (combined pharmaceuticals) in order to alleviate the gastric irritation resulting from the NSAID.

The gastroprotective (e.g. against gastritis, especially ulcerative) use of CGRP is known in the prior art. For example, Evans et al., U.S. Pat. No. 4,530,838 (7/85) discloses Calcitonin Gene Related Peptide (CGRP) and homologoues thereof for lowering gastric acid secretion in mammals (including humans) upon administration (e.g. orally intranasal: e.g. see col. 9 and patent claims, especially claims 7-9). Additionally, Gray et al, Annals of Surgery, Vol. 219 No. 1 pages 58-64 discloses the role of CGRP in protecting against gastric ulceration in a rat model (e.g. see pages 59-62 and DISCUSSION). The use of NSAID's to treat inflammatory diseases (e.g. rheumatism) and pain and the adverse side effects thereof (e.g. stomach inflammation; e.g. ulcers) is also known in the art (e.g. see column 1 of Gheczy et al, U.S. Pat. No. 4,528,193 (7/85). Further, the antiulcer activity of CGRP in rats, in general, and particularly with regard to alleviating ulcers which resulted from the administration of NSAID's (e.g. indomethacin and acetylsalicylic acid) is

disclosed by CAPLUS AN 1987:79162 to Maggi et al., Gen. Pharm. (1987) Vol. 18(1) pages 33-4. Accordingly, it would have been obvious at the time of applicant's invention to utilize an amylin agonist (e.g. CGRP) alone to alleviate stomach inflammation (e.g. gastritis, ulcers etc.) or concomitantly (e.g. in combined pharmaceuticals or in separate administrations) with NSAID's in order to alleviate the undesirable side effects of NSAIDS (e.g. stomach inflammation and/or ulcers), as disclosed in the above references, with a reasonable expectation of success.

8. Claims 1-3 and 5-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evans et al., U.S. Pat. No. 4,530,838 (7/85), Gray et al, Annals of Surgery, Vol. 219 No. 1 pages 58-64, CAPLUS AN 1987:79162 to Maggi et al., Gen. Pharm. (1987) Vol. 18(1) pages 33-4 and Bates et al., Br. J. Of Pharmacology Vol. 67(3) (Nov. 1979) pages 483P-484P in view of the Specification admission as to prior art on page 6, Kolterman et al., WO 95/07098 (3/95) and WPIDS Abstract No. 98-019088 to Liu et al. CN 1133718 (10/96), taken separately or in combination.

The presently claimed invention encompasses the use of "amylin" and amylin agonists" for their gastric protective effect (e.g. treat gastritis or gastric ulceration) alone or combined with a nonsteroidal antiinflammatory agent (combined pharmaceuticals) in order to alleviate the gastric irritation resulting from the NSAID.

The gastroprotective (e.g. against gastritis, especially ulcerative) use of CGRP (an amylin agonist) is known in the prior art. For example, Evans et al., U.S. Pat. No. 4,530,838 (7/85)

discloses Calcitonin Gene Related Peptide (CGRP) and homologoues thereof for lowering gastric acid secretion in mammals (including humans) upon administration (e.g. orally intranasal: e.g. see col. 9 and patent claims, especially claims 7-9). Additionally, Gray et al, Annals of Surgery, Vol. 219 No. 1 pages 58-64 discloses the role of CGRP in protecting against gastric ulceration in a rat model (e.g. see pages 59-62 and DISCUSSION). Further, the antiulcer activity of CGRP in rats, in general, and particularly with regard to alleviating ulcers which resulted from the administration of NSAID's (e.g. indomethacin and acetylsalicylic acid) is disclosed by CAPLUS AN 1987:79162 to Maggi et al., Gen. Pharm. (1987) Vol. 18(1) pages 33-4. Similarly, Bates et al. disclose the use of a calcitonin (e.g. salmon calcitonin) for its gastroprotective effects in the prevention/treatment of indomethacin (e.g. NSAID) induced gastric ulceration in the rat. Accordingly, it would have been obvious at the time of applicant's invention to utilize an amylin agonist (e.g. calcitonin and/or CGRP) alone to alleviate stomach inflammation (e.g. gastritis, ulcers etc.) or concomitantly (e.g. in combined pharmaceuticals or in separate administrations) with NSAID's in order to alleviate the undesirable side effects of NSAIDS (e.g. stomach inflammation and/or ulcers), with a reasonable expectation of success. However, the above references fail disclose the use of amylin or its analogues for their use for treating gastritis (or ulceration) alone or combined with NSAID's to alleviate the NSAID's side effects.

Both Amylin and amylin agonists are known to potently inhibit gastric emptying in rats, dogs and humans, especially use of the amylin agonist analogue AC187 (tri-Pro-amylin) (e.g. see specification at page 6). Similarly, Kolterman et al. reference disclose the administration of

"amylin" or "amylin agonists", especially "amylin agonist analogues" which are preferred (e.g. see pages 29-30) and tri-pro h-amylin which is most preferred (see tripro 25,28,29 human amylin, AKA AC-0137: See e.g. page 21 under "Summary of the Invention") for reducing gastric motility and slowing gastric emptying (e.g. See Abstract and PCT claims). Accordingly, the specification admission and/or the Kolterman reference establish the *functional equivalency* between amylin, amylin agonists (e.g. calcitonin and CGRP) and amylin analogues in effecting gastric activity (e.g. gastric motility and emptying). It is also noted that CGRP and Amylin share a high degree of homology (e.g. 50% homology). Still further, it is noted that the WPIDS Abstract discloses a pharmaceutical composition comprising amylin which when administered to a human cures gastrosis (e.g. gastritis and gastric ulcer) with a 90% total effective rate and a 50% cure rate without toxic side effects. Accordingly, the specification, the Kolterman reference and the WPIDS Abstract, taken separately, or in combination, teach the functional equivalency of amylin and its agonists, including amylin agonist analogues in effecting gastric functions including emptying, motility and anti-inflammation. Thus, the skilled artisan would have a reasonable expectation to expect that amylin and its analogues (e.g. tri-Pro amylin) would act similarly to amylin analogs (e.g. calcitonin and CGRP) which were shown in the primary references to possess gastric protective activity (e.g. anti-ulcer or anti-inflammatory activity). Accordingly, it would have been prima facie obvious to the skilled artisan at the time of applicant's invention to substitute amylin and its analogues for amylin agonist (e.g. CGRP and calcitonin) to obtain pharmaceuticals containing amylin or analogues thereof for their expected use in

preventing/treating gastritis or ulceration alone or combined with NSAID"S in order to alleviate the NSAID"s known side-effects (e.g. stomach inflammation, ulcers etc.) in view of the primary reference teaching of the amylin agonists use as antiulcer agents and the secondary references teachings of the functional equivalency of amylin agonists and amylin and its analogues in effecting gastric function .

9. Claims 4-8 and 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Young, U.S. Pat. No. 5,677,279 (10/97: filed 12/96) and Ghyczy et al., . U.S. Pat. No. 4,528,193 (7/85). The presently claimed invention is directed to combined pharmaceuticals of amylin and agonists thereof with NSAID's (e.g. acetaminophen) (e.g. see claims 11-12) and use thereof in analgesia (e.g. enhanced analgesia: see claim 4). Young et al., disclose the ability of amylin and its agonists alone to effect pain relief or the combination of amylin (or its agonists: including analogs and tri-pro amylin as most preferred) with "other pain relief agent" to further enhance pain relief (e.g. promote analgesia). See '279 abstract; columns 5-6 and patent claims 1 and 22. Although, the '279 patent specifically targets "narcotic analgesics" as its preferred pain reliever to be combined with amylin to effect "synergistic" pain relief, the '279 patent provides explicit motivation for combining "other pain relief agents" with amylin (or agonists thereof). The use of NSAID's (e.g. aspirin etc.) as pain relievers is conventionally known in the art.(e.g. see Gheczy et al, U.S. Pat. No. 4,528,193 (7/85). The making of pharmaceuticals and the determination of optimum delivery dosages and means of administration is within the skill of the art. It would have

been prima facie obvious to the skilled artisan at the time of applicant's invention to combine amylin or its agonists with NSAID's in order to effect "enhanced analgesia" with a reasonable expectation of success since the prior art recognized the separate analgesic utility of amylin and NSAID's which would motivate the skilled artisan to make combination pharmaceuticals thereof and in view of the express motivation presented in the '279 patent to do so.

Double Patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 4-8 and 10-12 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-22 (especially patent claim 22) of U.S. Patent No. 5,677,279 in view of Ghyczy et al., . U.S. Pat. No. 4,528,193 (7/85). . Young et al., disclose AND claim amylin (and its agonists) to effect pain relief alone or combined with "other pain relief agent".. See '279 abstract; columns 5-6 and patent claims 1 and 22. The use of NSAID's (e.g. aspirin etc.) as pain relievers is conventionally known in the art.(e.g. see Gheczy et

al, U.S. Pat. No. 4,528,193 (7/85). The making of pharmaceuticals and the determination of optimum delivery dosages and means of administration is within the skill of the art. It would have been prima facie obvious to the skilled artisan at the time of applicant's invention to combine amylin or its agonists with NSAID's in order to effect "enhanced analgesia" with a reasonable expectation of success since the patent claims recognized the separate and combined analgesic utility of amylin and pain relievers (e.g. NSAID's as disclosed in Ghyczy et al.) which would motivate the skilled artisan to make combination pharmaceuticals of amylin (or agonists) with NSAID's with a reasonable expectation of enhancing analgesia.

General information regarding further correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Celsa whose telephone number is (703) 305-7556.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can be reached at (703)308-0254.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Bennett Celsa

June 8, 1998